

REMARKS

In the Office Action, the Examiner (1) withdrew claims 51-67 from further consideration as being directed to a non-elected invention, (2) withdrew various objections and rejections raised in the previous office action, (3) maintained the indefiniteness rejection under 35 U.S.C. §112, second paragraph against claim 47, (4) rejected claims 10-14 and 41-50 under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement, and (5) rejected claims 10-14 and 41-50 under 35 U.S.C. §102(b) as being anticipated by Kozaki et al. (Microbial Pathogenesis, 1998, 25:91-99). Each rejection raised by the Examiner is addressed separately below. In view of the amendments noted above and the remarks below, applicants respectfully request reconsideration of the merits of this patent application.

No extension of time is believed to be necessary and no fee is believed to be due in connection with this response. However, if any extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to Deposit Account No. 17-0055. No other fee is believed to be due in connection with this response. However, if any fee is due in this or any subsequent response, please charge the fee to the same Deposit Account No. 17-0055.

Election/Restriction

Applicants acknowledge that claims 51-67 are withdrawn from further consideration and respectfully note that they will be eligible for rejoinder once the corresponding complex claims are found allowable as claims 51-67 are directed at methods of forming the complexes.

Indefiniteness rejection under 35 U.S.C. §112, second paragraph

The Examiner maintained the indefiniteness rejection against claim 47 alleging that it is unclear as to whether applicants are claiming an organism such as a rat, mouse or human in claim 47 by reciting "wherein the polypeptide is located in vivo." In response to the applicants' clarification and amendment that the claim does not cover an organism but rather a complex that is formed in vivo in a mammal, the Examiner alleged that it is unclear as how the complex is formed *in vivo*. While not agreeing with the rejection because a skilled artisan can readily form such a complex *in vivo* by administering a polypeptide defined in claim 10 and an antibody to the polypeptide into a mammal, applicants have amended claim 47 to specify "wherein the complex

is located *in vivo*." In addition to the case mentioned above wherein the complex is formed *in vivo*, a complex can also be located *in vivo* by administering (*e.g.*, by intravenous injection) a complex formed *in vitro* to an animal in a manner similar to that provided at lines 12-14 of paragraph [00063] of the application.

Claim 47 depends on claim 45 which in turn depends on claim 10. Therefore, claim 47 incorporates all the limitations of claims 10 and 45. As it is clear from claim 10, what is being claimed is a complex of a ligand and a polypeptide (the polypeptide is defined in detail in claim 10), not an organism such as a rat, mouse or human. Claim 45 as amended further limits the ligand to an antibody that binds to the BoNT/B-binding domain. Accordingly, it is clear that claim 47 is directed at a complex of the polypeptide and its antibody rather than an organism such as a rat, mouse or human. Withdraw of the indefiniteness rejection is respectfully requested.

Written description rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 10-14 and 41-50 as failing to comply with the written description requirement, alleging that the specification does not describe a substantial number of the members of the ligand-polypeptide complex genus to reasonably convey to the skilled artisan that applicants had possession of the claimed invention. In particular, the Examiner alleged that the specification does not describe (1) a complex of a ligand and a polypeptide that is homologous or at least 70%, 80%, 90%, or 95% identical to amino acids 40-60 of a murine synaptotagmin II, (2) which botulinum toxin serotype B (BoNT/B) fragment binds to the BoNT/B binding domain of a murine synaptotagmin II, (3) how one would form the complex *in vivo*, and (4) a correlation between the complex and reduced binding activity between BoNT/B and murine synaptotagmin II.

Without agreeing with the rejection, applicants have amended claims 10 and 45 and reserve the right to pursue the canceled subject matter in a continuation application. As amended, the ligand recited in the claims at issue is limited to botulinum toxin serotype B (BoNT/B) or an antibody that binds to a murine synaptotagmin II protein at amino acids 40-60 or an equivalent defined in claim 10. Applicants respectfully traverse the rejection in connection with the claims as amended.

With respect to point (1) above, the specification supports an antibody that binds to a murine synaptotagmin II protein at amino acids 40-60 or an equivalent defined in claim 10 (*see e.g.*, end of paragraph [00011]). As will be discussed in detail below, since the polypeptides recited in claim 10 have been described by their structure, it is routine to make antibodies against the polypeptides and a skilled artisan appreciates that the polypeptides and their antibodies can form a complex. A complex of BoNT/B and the polypeptide defined in claim 10 is also supported by the specification (*see e.g.*, paragraph [00037], lines 1-5).

On the polypeptide side of the complex, applicants respectfully submit that synaptotagmin II is a well known protein. The structure of synaptotagmin II is also well known in the art. For example, as provided in the specification, synaptotagmin II contains a luminal domain, a transmembrane domain, and a cytoplasmic domain, which contains two C2 domains: C2A and C2B linked by a linker region (*see* paragraph [0007]). The amino acid sequences of synaptotagmin II from rat, mouse, and human are available in the art (*see* paragraph [00024] of the application) and they all share the same structures as described above as well as a high degree of homology. For example, the mouse, rat, and human synaptotagmin II proteins are over 90% identical at the BoNT/B binding domain. Given that synaptotagmin II is a well known protein with well known structures and the specification provides the amino acid sequences of synaptotagmin II from three species (SEQ ID NO:7, 9, and 10 for mouse, rat, and human, respectively), the written description requirement for the genus of synaptotagmin II homologs is met. Further, given the conserved structures, a skilled artisan can readily identify the BoNT/B binding domain on a synaptotagmin II protein in view of the BoNT/B binding domain taught by the present invention.

As far as polypeptides that are at least 70%, 80%, 90%, or 95% identical to amino acids 40-60 of a murine synaptotagmin II are concerned, contrary to the Examiner's allegation that the instant specification only described complexes that comprises amino acids 1-267, 61-26, and 1-87 of synaptotagmin II, the specification described complexes that comprises polypeptides that are at least 70%, 80%, 90%, or 95% identical to amino acids 40-60 of a murine synaptotagmin II protein. For example, paragraph [00037] of the application provides that polypeptides that are at least 70%, 80%, 90%, or 95% identical to amino acids 40-60 of a murine synaptotagmin II can compete with synaptotagmin II for BoNT/B binding.

Applicants also respectfully submit that polypeptides that are at least 70%, 80%, 90%, or 95% identical to amino acids 40-60 of a murine synaptotagmin II have been described by their structure, *i.e.*, their amino acid sequences. The amino acid sequences of murine (mouse and rat) synaptotagmin II proteins are provided in the application as SEQ ID NO:7 and SEQ ID NO:9, respectively. A skilled artisan can certainly envision the amino acid sequences that are at least 70%, 80%, 90%, or 95% identical to amino acids 40-60 of SEQ ID NO:7 or SEQ ID NO:9. This is the same as when a polypeptide is described as SEQ ID NO:X with a substitution mutation at amino acid position 1, the written description requirement is met as the polypeptide has been described by its structure (the amino acid sequence). It is acknowledged that the number of the polypeptides that are at least 70%, 80%, 90%, or 95% identical to amino acids 40-60 of a murine synaptotagmin II is large. However, this does not mean that the written description requirement is not satisfied. A skilled artisan can envision all these sequences. For any given polypeptide, there will no confusion as to whether it is at least 70%, 80%, 90%, or 95% identical to amino acids 40-60 of SEQ ID NO:7 or SEQ ID NO:9. Accordingly, the written description requirement for these polypeptides is met as their structures have been described.

The inventors of the instant invention pinpointed the BoNT/B binding domain of murine Syt II proteins through a series of structural and functional experiments (*see e.g.*, paragraphs [00067], [00068], [00071]-[00073], [00077], and [00078]) and a skilled artisan appreciates that many polypeptides having 70% or higher identity to the BoNT/B binding domain will also be able to bind to BoNT/B. Accordingly, a skilled artisan would clearly recognize that the inventors had possession of the invention as claimed. It would not be commensurate with the contribution the inventors made to the art if one is allowed to avoid the claims literally by simply making one conservative substitution on the BoNT/B binding domain.

With respect to point (2) above, claims 10 and 45 have been amended to delete the subject matter of BoNT/B fragments. This point is believed to have been rendered moot.

With respect to points (3) and (4) above, applicants respectfully submit that it is well within the capability of a skilled artisan to form the complex *in vivo*. With the BoNT/B receptor and its BoNT/B binding domain identified by the inventors, a skilled artisan appreciates that an antibody to the binding domain can be administered into an animal, for example in a manner similar to that provided at lines 12-14 of paragraph [00063] of the application, and the antibody will bind to the receptor *in vivo* to form a complex. As a result, BoNT/B will not be able to bind

to the receptors occupied by the antibody and the toxicity will be reduced. A skilled artisan also appreciates that a polypeptide defined in claim 10 can be administered into an animal having *Clostridium botulinum* infection, for example in a manner similar to that provided at lines 12-14 of paragraph [00063] of the application, and the polypeptide will bind to BoNT/B *in vivo* to form a complex. As a result, BoNT/B bound by the polypeptide will not be able to bind to its receptor located on the surface of a cell to enter the cell and the toxicity is reduced. It is well within the capability of a skilled artisan to administer an antibody or a polypeptide into an animal. For the purpose of the written description requirement, what is conventional or well known to a skilled artisan need not be disclosed in detail (*see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986)).

In summary, claims 10 and 45 have been amended to further limit the complex recited in the claims at issue. The polypeptide part of the complex has been described by their distinguishing identifying characteristics, i.e., being homologous or at least 70%, 80%, 90%, or 95% identical to amino acids 40-60 of SEQ ID NO:7 or 9 (murine synaptotagmin II). Sufficient and/or representative number of species have also been described given that synaptotagmin II is a well known protein highly conserved across animal species and a skilled artisan can envision the exact amino acid sequences that are at least 70%, 80%, 90%, or 95% identical to amino acids 40-60 of SEQ ID NO:7 or 9. On the ligand side, BoNT/B is well known in the art and the specification describes that the polypeptide defined in claim 10 can bind to BoNT/B. The antibody has also been described by its distinguishing identifying characteristic, i.e., the ability to bind to particular amino acid sequences. It is routine in the art to generate corresponding antibodies to a polypeptide with its amino acid sequence known and it is customary in the art to describe antibodies by their target amino acid sequences. Therefore, the complex encompassed by the claims as amended has been described by its distinguishing identifying characteristics and in view of the description a skilled artisan would understand that the applicants were in possession of the invention at the time the application was filed. Accordingly, the written description requirement for the amended claims is satisfied.

Anticipation rejections under 35 U.S.C. §102 (b)

The Examiner rejected claims 10-14 and 41-50 under 35 U.S.C. §102(b) as being anticipated by Kozaki et al. (Microbial Pathogenesis, 1998, 25:91-99). In making the rejection,

the Examiner alleged that Kozaki et al. teach a complex of MBP-Stg2N (a fusion protein of maltose binding protein (MBP) and amino acids 1-87 of the rat synaptotagmin II (Stg2N)) and botulinum toxin serotype B (BoNT/B). Applicants respectfully traverse the rejection.

Claims 10-14 and 41-50 as amended are directed at a complex of a ligand and a polypeptide, wherein the polypeptide comprises an amino acid sequence that is homologous or at least 70% identical to a murine synaptotagmin II botulinum toxin serotype B (BoNT/B)-binding domain at amino acid position 40 to 60, wherein the ligand is selected from the group consisting of BoNT/B and an antibody against said amino acid sequence, and wherein the ligand binds to the polypeptide at said amino acid sequence (i.e., an amino acid sequence that is homologous or at least 70% identical to a murine synaptotagmin II botulinum toxin serotype B (BoNT/B)-binding domain at amino acid position 40 to 60), with the proviso that where the polypeptide is a full length synaptotagmin, the ligand is not a botulinum toxin.

While disclosing a complex of MBP-Stg2N (containing amino acids 1-87 of the rat synaptotagmin II) and BoNT/B, Kozaki et al. do not specifically teach that in their complex BoNT/B binds to amino acids 40-60 of synaptotagmin II as required by the claims at issue. In fact, in another paper from the same group (Nishiki et al. FEBS Letters 378:253-257, 1996, which is of the record in this case), the authors indicated that in their system BoNT/B binds to amino acids 1-20 of synaptotagmin II (see the paragraph bridging the left and right columns of page 255).

Kozaki et al. also disclosed a complex of an antibody and MBP-Stg2N (Fig. 1 and relevant text). However, the reference does not specifically teach that the antibody binds to amino acids 40-60 of synaptotagmin II as required by the claims at issue. In fact, said other paper from the same group (Nishiki et al. FEBS Letters 378:253-257, 1996) indicated that one of the two antibodies used, ST209, binds to amino acids 9-14 of synaptotagmin II (Fig. 6 and the paragraph bridging the left and right columns of page 255).

In summary, Kozaki et al. do not teach the limitation of claims 10-14 and 41-50 which requires that a ligand binds to synaptotagmin II at amino acids 40-60 or an equivalent thereof. Another paper published by the same group indicates that in the systems employed by Kozaki et al. BoNT/B and the antibodies bind to amino acids 1-20 and 9-14, respectively. Therefore, Kozaki et al. cannot anticipate claims 10-14 and 41-50.

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Claim 44 is limited to a complex wherein the polypeptide consists of the BoNT/B-binding domain of synaptotagmin II (*e.g.*, amino acids 40-60 of rat synaptotagmin II). Since the complex disclosed by Kozaki et al. (*e.g.*, amino acids 1-63 and amino acids 1-87) contains extra amino acids, claim 44 is not anticipated by Kozaki et al. further for this reason.

Summary

Having addressed each rejection raised by the Examiner, the claims as amended are believed to be in condition for allowance and a Notice of Allowance is respectfully requested. Should any issues remain outstanding, the Examiner is invited to contact the undersigned at the telephone number appearing below if such would advance the prosecution of this application.

Respectfully submitted,



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